Sagely Health

YOUR PERSONALIZED PATHFINDER REPORT

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PREPARED FOR

Jane Doe (Sample Patient)

Metastatic Pancreatic Cancer

PATIENT SUMMARY

Jane is a 60-year-old woman with AJCC Stage IV Pancreatic Adenocarcinoma with metastases in the liver. She comes to Sagely Health in search of guidance on her treatment regimen.

In December of 2019, Jane presented with jaundice, and was diagnosed with borderline resectable pancreatic adenocarcinoma. She was initially treated with 6 cycles of FOLFIRINOX from January 2020-May 2020. This was followed by an exploratory laparotomy/cholecystectomy that deemed her unresectable in June 2020. She received FOLFIRINOX for 4 cycles from December 2020 through February 2021, followed by two cycles of FOLFIRI in February. After that, she enrolled on a clinical trial for tumor sequencing. Jane received radiotherapy (x 28 fractions) and gemcitabine weekly in April 2021. In July 2021 she underwent a whipple surgery with a diagnosis of Stage IIA. On the subsequent scan, a liver metastasis was discovered.

She has come to Sagely Health seeking innovative therapy options. She is able to travel and receive treatment throughout the United States, but prefers her home in the Northeastern US.

Sequencing Results:
KRAS (G12V), p53, SMAD4, and LZTR,
Tumor Mutational Burden: Low
Microsatellite Stable (MSS)
PD-L1: 0% (negative)

OUR APPROACH

Sagely Health owns, operates, and maintains an up-to-the-minute cancer therapy recommendation engine. Our searches factors in patient details (as reported to us) along with real-time scientific findings. A series of searches were performed for this patient and an expert oncologist has analyzed the results to arrive at our recommendations. Each recommendation has a scientific rationale included.

OUR FINDINGS

Following a search of all available therapies and relevant published patient data, we selected 3 clinical trials that appear to have early results that are promising, and as a result, we recommend exploring them with your Oncologist and seeking a second opinion from the doctors referenced in the report. We have included questions to facilitate access to these as well as other ideas that could produce Jane's best possible outcome. Please contact us with any questions at info@sagelyhealth.com.

Best wishes,
Jason Sager, MD

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Chemotherapy and Immunotherapy Combination | NCT03214250

Safety and Efficacy of APX005M With Gemcitabine and Nab-Paclitaxel With or Without Nivolumab in Patients with Newly Diagnosed Metastasis of Pancreatic Adenocarcinoma

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Phase 1 Trial of Interleukin 12 Gene Therapy for Metastatic Pancreatic Cancer

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Chemotherapy, Immunotherapy, and Other Combination | NCT02754726

A Phase II Pilot Trial of Nivolumab + Albumin-Bound Paclitaxel + Paricalcitol + Cisplatin + Gemcitabine (NAPPCG) In Patients With Newly Diagnosed Metastasis of Pancreatic Ductal Adenocarcinoma

HonorHealth Research Institute

1 Safety and Efficacy of APX005M With Gemcitabine and Nab-Paclitaxel With or Without Nivolumab in Patients with Newly Diagnosed Metastasis of Pancreatic Adenocarcinoma

THERAPY TYPE: Chemotherapy and Immunotherapy Combination

REFERENCE: NCT03214250

Randomized	Not Blinded	No Placebo
You will be randomly assigned to receive a specific treatment.	You will be told what treatment you are receiving.	There is no placebo used in this trial.

WHERE TO GO

Memorial Sloan Kettering Cancer Center
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WHO TO CONTACT

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WHY IS THIS OF INTEREST?

In patients with metastatic pancreatic cancer, the 1-year overall survival rate for patients receiving APX005M in the combination ranged from 41% (gem/NP/nivo/APX005M) to 57% (gem/NP/APX005M). These are greatly improved from the approximate 5% historical 1 yr overall survival rate for gemcitabine and nab-paclitaxel alone.

WHAT YOU SHOULD ALSO KNOW

APX005M is generally well-tolerated with the most common adverse reactions being fatigue and nausea. There are significant side effects with the chemotherapy portion and about 15% of patients experience intolerable side-effects of nivolumab. This trial is randomized, but not blinded, so you will know which therapies you are receiving, though not able to control which you would get.

HOW DOES IT WORK?

Nivolumab (Intravenous) - Nivolumab is an anti-PD-1 antibody, also known as a checkpoint inhibitor, that aims to expose a tumor as foreign so that the body's immune system can attack it. Some cancerous cells express PD-L1 that attach to PD-1, effectively inactivating the immune cell's ability to recognize the tumor cells. Nivolumab disrupts this inactivation, enabling the immune system to work properly.

Nab-paclitaxel (Intravenous) - Nab-paclitaxel is a protein-bound form of paclitaxel. The attached protein is used as a transportation vehicle, expediting the delivery of the drug to the cancer. Specifically, nab-paclitaxel is bound to the blood protein albumin, labeling it nanoparticle albumin-bound (nab). Paclitaxel (taxol) is a chemotherapy agent that works by stopping cancer cells from separating into two new cells which helps to block the growth of the cancer.

Gemcitabine Hydrochloride (Intravenous) - Gemcitabine is a chemotherapy agent that inhibits DNA synthesis. The loss of DNA synthesis results in cancer cell death.

APX005M (Intravenous) - APX005M is a humanized monoclonal antibody agonist of the cell surface receptor CD40. Similar to the endogenous CD40 ligand (CD40L or CD154), CD40 agonistic monoclonal antibody APX005M binds to CD40 on a variety of immune cell types. This triggers cellular proliferation which results in an enhanced immune response against tumor cells.

SCIENTIFIC/TECHNICAL INFORMATION

Gemcitabine (Gem) and nab-paclitaxel (NP) ± nivolumab (nivo) ± CD40 agonistic monoclonal antibody APX005M (Sotigalimab), in patients (Pts) with untreated metastatic pancreatic adenocarcinoma (mPDAC): Phase (Ph) 2 final results.

View Source Online

SCAN FOR LINK

Background: Results from a ph1b trial evaluating gem/NP with CD40 agonistic monoclonal antibody APX005M ± nivo demonstrated promising clinical activity in pts with untreated mPDAC (O'Hara 2021). Herein, we report results from the follow-on, randomized (rand) ph2 trial evaluating gem/NP ± nivo ± APX005M. Methods: Pts with untreated mPDAC were rand to 1 of 3 open-label arms: gem/NP/nivo (A), gem/NP/APX005M (B), gem/NP/nivo/APX005M (C). All pts were treated with 1000 mg/m2 gem and 125 mg/m2 NP. Patients received 240 mg nivo in arms A and C and 0.3 mg/kg APX005M (RP2D) IV in arms B and C. Ph1b pts were included in ph2 analyses. 1° endpoint: 1-year OS rate of each arm, compared to a 35% historical OS rate for gem/NP (Von Hoff 2013). Key 2° endpoints: ORR, DCR, DOR, PFS and safety. Tumor and blood were collected for biomarker analysis. Planned enrollment of 35 pts/arm provided 81% power for testing the alternative of 58% OS rate vs 35%, using a 1-sided, 1-sample Z test with 5% type I error. Trial was not powered for cross-arm comparison. Results: 93 pts were rand in ph2 (N = 34, 30, 29 to A, B, C); when ph1b pts included, a total of 105 pts (34, 36, 35) were analyzed for efficacy and 108 pts (36, 37, 35) for safety. Min follow-up was 14 months (mos). Baseline characteristics were balanced across arms, inclusive of tumor burden, presence of liver metastases and stage at initial diagnosis (stage 1-3 vs 4). 1-year OS rate was 57% (1-sided p = 0.007 vs 35% historical rate, 95% lower CI bound = 41%) for A, 51% (p = 0.029, 95% bound = 36%) for B and 41% (p = 0.236, 95% bound = 27%) for C. Median OS and secondary endpoints are listed in Table. TRAE rates were similar across arms and to ph1b. 8 (7%) pts experienced an AE leading to tx discontinuation (6, 1, 1 in A, B, C), 40 (37%) pts experienced a serious TRAE (14, 15, 11 in A, B, C) and 2 pts died due to TRAEs; 1 each in B (acute hepatic failure) and C (intracranial hemorrhage). Conclusions: In this ongoing, seamless ph1b/2 trial of gem/NP ± nivo ± APX005M in pts with mPDAC, antitumor activity was observed in all arms. 1° endpoint of 1-year OS > 35% was met when combining gem/NP with either nivo or APX005M; however, not the combination. Safety was manageable; consistent with ph1b. Detailed multiomic immune and tumor biomarker analyses are underway to elucidate mechanisms of action and inform pt subsets that benefit most from these combinations. Clinical trial information: NCT03214250.

% (n) [95% CI]	A (n = 34)	B (n = 36)	C (n = 35)
ORR*	50 (17) [32–68]	33 (12) [19–51]	31 (11) [17–49]
ORR (confirmed)*	35 (12) [20–54]	33 (12) [19–51]	26 (9) [13–43]
DCR	74 (25) [56–87]	78 (28) [61–90]	69 (24) [51–83]
Median DOR, mos	4.8 [2.5–NE]	5.5 [3.7–7.6]	6.6 [1.9–NE]
Median PFS, mos	6.3 [5.2–8.8]	7.2 [5.3–9.2]	6.7 [4.1–9.8]
Median OS, mos	16.7 [9.8–20.4]	14.5 [7.2–20.1]	10.1 [7.9–13.2]
1-year OS, % [p]	57 [0.007]	51 [0.029]	41 [0.236]

2 Phase 1 Trial of Interleukin 12 Gene Therapy for Metastatic Pancreatic Cancer

THERAPY TYPE: Immunotherapy and Chemotherapy Combination

REFERENCE: NCT03281382

Not Randomized	Not Blinded	No Placebo
You will not be randomly assigned to receive a specific treatment.	You will be told what treatment you are receiving.	There is no placebo used in this trial.

WHERE TO GO

Josephine Ford Cancer Center at Henry Ford Hospital
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WHO TO CONTACT

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WHY IS THIS OF INTEREST?

In patients with metastatic pancreatic cancer, Interleukin-12 gene therapy has demonstrated benefit at the highest dose level given (at the time of publication): 4 of the 6 patients who received it were still alive, on average with 18.1 month follow-up.

WHAT YOU SHOULD ALSO KNOW

Interleukin-12 gene therapy is generally well-tolerated with mostly mild or moderate side effects. This trial also includes chemotherapy, which is expected to have known side effects.

HOW DOES IT WORK?

Interleukin-12 Gene Therapy (Intratumoral) - Interleukin-12 gene therapy activates antitumoral natural killer (NK) cells and CD8+ T-cells and stimulates the secretion of interferon-gamma (IFN-gamma), potentially inhibiting tumor cell metastasis. This gene therapy may also result in IL-12-mediated inhibition of vascular endothelial growth factor (VEGF).

5-Fluorocytosine (Oral) - 5-fluorocytosine is a drug known as an antimetabolite. It works by stopping cancer cells from making and repairing DNA, leading to cell death.

SCIENTIFIC/TECHNICAL INFORMATION

Phase I trial of oncolytic adenovirus-mediated cytotoxic and interleukin-12 gene therapy for the treatment of metastatic pancreatic cancer

View Source Online

SCAN FOR LINK

The safety of oncolytic adenovirus-mediated suicide and interleukin-12 (IL12) gene therapy was evaluated in metastatic pancreatic cancer patients. In this phase I study, a replication-competent adenovirus (Ad5-yCD/mutTKSR39rep-hIL-12) expressing yCD/mutTKSR39 (yeast cytidine deaminase/mutant S39R HSV-1 thymidine kinase) and human IL-12 (IL12) was injected into tumors of 12 subjects with metastatic pancreatic cancer (T2N0M1-T4N1M1) at escalating doses (1 × 1011, 3 × 1011, or 1 × 1012 viral particles). Subjects received 5-fluorocytosine (5-FC) therapy for 7 days followed by chemotherapy (FOLFIRINOX or gemcitabine/albumin-bound paclitaxel) starting 21 days after adenovirus injection. The study endpoint was toxicity through day 21. Experimental endpoints included measurements of serum IL12, interferon gamma (IFNG), and CXCL10 to assess immune system activation. Peripheral blood mononuclear cells and proliferation markers were analyzed by flow cytometry. Twelve patients received Ad5-yCD/mutTKSR39rep-hIL-12 and oral 5-FC. Approximately 94% of the 121 adverse events observed were grade 1/2 requiring no medical intervention. Ad5-yCD/mutTKSR39rep-hIL-12 DNA was detected in the blood of two patients. Elevated serum IL12, IFNG, and CXCL10 levels were detected in 42%, 75%, and 92% of subjects, respectively. Analysis of immune cell populations indicated activation after Ad5-yCD/mutTKSR39rep-hIL-12 administration. The median survival of patients in the third cohort is 18.1 (range, 3.5–20.0) months. The study maximum tolerated dose (MTD) was not reached.

3 A Phase II Pilot Trial of Nivolumab + Albumin-Bound Paclitaxel + Paricalcitol + Cisplatin + Gemcitabine (NAPPCG) In Patients With Newly Diagnosed Metastasis of Pancreatic Ductal Adenocarcinoma

THERAPY TYPE: Chemotherapy, Immunotherapy, and Other Combination

REFERENCE: NCT02754726

Not Randomized	Not Blinded	No Placebo
You will not be randomly assigned to receive a specific treatment.	You will be told what treatment you are receiving.	There is no placebo used in this trial.

WHERE TO GO

HonorHealth Research Institute
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WHO TO CONTACT

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WHY IS THIS OF INTEREST?

This combination regimen (NAPPCG) was shown to be beneficial in patients with metastatic pancreatic cancer: Out of 10 patients, 8 patients experienced significant tumor shrinkage (called a partial response) and 2 had cancer control (stable disease) leading to an overall response rate of 80%. Duration of cancer control for all 10 patients was approximately 8 months on average.

WHAT YOU SHOULD ALSO KNOW

The most common severe side effects of this NAPPCG combination were low platelets in all 10 patients, but with no serious bleeding events; anemia in 50% of patients, and lower GI (colon) bleeding (called colitis) in 20% of patients. Colitis is a known effect of nivolumab which is commonly reversed with a short course of glucocorticoids if it occurs.

HOW DOES IT WORK?

Nivolumab (Intravenous) - Nivolumab is an anti-PD-1 antibody, also known as a checkpoint inhibitor, that aims to expose a tumor as foreign so that the body's immune system can attack it. Some cancerous cells express PD-L1 that attach to PD-1, effectively inactivating the immune cell's ability to recognize the tumor cells. Nivolumab disrupts this inactivation, enabling the immune system to work properly.

Nab-paclitaxel (Intravenous) - Nab-paclitaxel is a protein-bound form of paclitaxel. The attached protein is used as a transportation vehicle, expediting the delivery of the drug to the cancer. Specifically, nab-paclitaxel is bound to the blood protein albumin, labeling it nanoparticle albumin-bound (nab). Paclitaxel (taxol) is a chemotherapy agent that works by stopping cancer cells from separating into two new cells which helps to block the growth of the cancer.

Paricalcitol (Intravenous) - Paricalcitol is a man-made form of vitamin D. It works by blocking a signal in the cancer cells that leads to growth and spreading of the tumor.

Cisplatin (Intravenous) - Cisplatin is a chemotherapy agent that works by preventing the repair of the DNA, leading to DNA damage and cancer cell death.

Gemcitabine Hydrochloride (Intravenous) - Gemcitabine is a chemotherapy agent that inhibits DNA synthesis. The loss of DNA synthesis results in cancer cell death.

SCIENTIFIC/TECHNICAL INFORMATION

A phase II pilot trial of nivolumab (N) + albumin bound paclitaxel (AP) + paricalcitol (P) + cisplatin (C) + gemcitabine (G) (NAPPCG) in patients with previously untreated metastatic pancreatic ductal adenocarcinoma (PDAC).

View Source Online

SCAN FOR LINK

Background: Effective therapy for the treatment of PDAC remains one of the greatest unmet oncology clinical needs. The addition of C to G and AP has shown promising clinical data in a previously reported study [J Clin Oncol 35, 2017 (suppl 4S; abstract 341)]. In preclinical work, vitamin D (Vit D) analog therapy decreases myeloid derived suppressor cells and regulatory T cells, turning PDAC into a more immune-friendly microenvironment. This trial combines AP/C/G with Vit D analog P and the anti-PD-1 antibody N as a combination therapy for patients with previously untreated metastatic PDAC. This trial evaluates the efficacy and safety of NAPPCG in that patient population (NCT02754726). Methods: Eligibility criteria include Stage IV PDAC, no prior chemotherapy for systemic disease, KPS ≥ 70, and measurable disease. Doses are AP 125 mg/m2 undiluted, G 1000 mg/m2 in 250 ml of normal saline (NS), each infused over 30 minutes with C 25 mg/ m2 in 500 ml of NS infused over 60 minutes on days 1, 8, 22, and 29 of a 42-day cycle. N is given at a fixed dose of 240 mg as a 60 minute infusion on days 1, 15, and 29. P is given at a fixed dose of 25 µg IV twice weekly. Primary objective is to determine the efficacy of the combination for patients with previously untreated metastatic PDAC through determining CR, ORR, PFS, and OS. The secondary objective is to evaluate safety in patients with previously untreated metastatic PDAC. Results: Trial was initiated May 2016 and10 patients have been enrolled in the initial phase of the study and are evaluable (baseline and ≥1 follow up CT scan). Most common drug-related grade (Gr) 3-4 adverse events (AE's), n = 10, are thrombocytopenia 100% (gr 3 = 50%, gr 4 = 50%) with no serious bleeding events, anemia 50% (gr 3 = 50%, gr 4 = 0%), and colitis 20% (gr 3 = 20%, gr 4 = 0%). By RECIST 1.1 criteria, the best response is 8 PR and 2 SD, yielding an 80% ORR. Median PFS is 8.2 months. Median OS has not been reached. Conclusions: Although a small study, the high response rate is encouraging. This regimen is being expanded to 25 patients with plans to include exploratory inflammatory biomarkers.

QUESTIONS FOR THE ONCOLOGIST/MEDICAL TEAM

Thank you for taking the time to answer these questions so Jane might achieve her best possible outcome. Please feel free to take notes directly or provide the answers to Jane when you next see her. We are always available to answer questions as well at info@saglelyhealth.com or phone at (844) 724-3591.

- [ ] **Given the single new metastasis, are there any local treatments (e.g. surgery, radiation, other) worth using to ablate the tumor (even if there are other micromets)?**

Response:

- [ ] **Given the low expectations from standard chemo, are the therapies included in this report worth considering?**

Response:

- [ ] **Do you have any that you think look particularly interesting and would recommend evaluating first?**

Response:

- [ ] **Is it worth checking and following CA-19-9, the circulating tumor marker? If negative, can the mutations be monitored via a liquid tumor biopsy?**

Response:

- [ ] **Is it worth obtaining another genetic analysis (tumor sequencing) to look for additional genetic alterations?**

  Response:

- [ ]

- [ ]

GLOSSARY OF COMMON TERMS

Adjuvant
Cancer treatment given after definitive surgery to lower the risk that the cancer will come back. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biological therapy.

Biopsy, Tumor
An examination of tissue removed from the body to discover the presence, cause, or extent of a tumor (cancer).

Clinical Trial
A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. Also called a clinical study.

Efficacy
Effectiveness. In medicine, the ability of an intervention (for example, a drug or surgery) to produce the desired beneficial effect.

Immunotherapy, Cancer
Immunotherapy uses a person's immune system to fight cancer. Some boost the body's immune system, while others train the immune system to attack the cancer cells.

Mechanisms of Action
Mechanism of action (MOA) refers to the way a therapy works. A mechanism of action usually includes mention of the specific molecular targets to which the drug attaches, such as an enzyme or receptor.

Metastatic
Metastasis is the spread of cancer cells to distant areas of the body (often by way of the lymph system or bloodstream). Metastatic cancer, or a metastatic tumor, is one which has spread from the primary site of origin (where it started) into different area(s) of the body.

Neoadjuvant
Treatment given as a first step to shrink a tumor before surgery. Examples of neoadjuvant therapy include chemotherapy, radiation therapy, and hormone therapy.

Pathology Report
The description of cells and tissues made by a pathologist based on microscopic evidence, and sometimes used to make a diagnosis of a disease.

Randomized Study
A study in which the participants are assigned by chance (randomly) to different groups that compare different therapies. This means that the patient or doctor does not get to pick the specific treatment. However, the patient may know which treatment they are getting (unless blinded) and almost all oncology trials do not treat patients with only placebo (sugar pill).

Recurrence or Recurrent Cancer
Cancer that has recurred (come back), usually after a period of time during which the cancer could not be detected. The cancer may come back in the same place as the original (primary) tumor or in another place in the body. Reference
A scientific publication (poster or journal article) related to the therapy being discussed.

Standard of Care
Treatment that is accepted by medical experts as being effective for a certain type of cancer and that is widely used by healthcare professionals. Also called standard medical care, and standard therapy.

Targeted Therapy
A type of treatment that attack specific types of cancer cells with less harm to normal cells. Some targeted therapies block the action of certain enzymes, proteins, or other molecules involved in the growth and spread of cancer cells. Targeted therapy may have fewer side effects than other types of cancer treatment.

Therapy
Any treatment for patients.

Tumor Sequencing
The study of a sample of DNA to look for mutations (changes) that may increase risk of disease or affect the way a person responds to treatment.